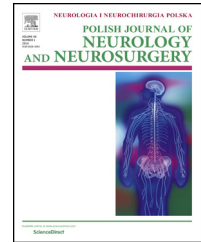


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Review article

Potential role of statins in the intracerebral hemorrhage and subarachnoid hemorrhage



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ABSTRACT

Statins are used in primary and secondary prevention of cardiovascular episodes. Most of recent studies regard ischemic stroke. There are more emerging results of studies suggesting usefulness of these drugs in the other types of stroke e.g. intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Searching for new methods of treatment is important, because both ICH and SAH lead to poor prognosis and severe psychomotor disability.

The unquestionable role of inflammatory factors in the pathogenesis of these disorders justifies considering statin treatment. Previous results are contradictory, thus in present study we review results of studies and try to explain the potential pathomechanism of statin use in hemorrhagic strokes.

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1. Introduction

Statins are used in primary and secondary prevention of cardiovascular episodes. Among neurological disorders they play a key role in ischemic stroke, but there are reports of possible beneficial effect of statins in dementia and multiple sclerosis [1–3].

Most of recent studies regard ischemic stroke. There are more emerging results of studies suggesting usefulness of this drugs in other types of stroke e.g. intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Searching for new methods of treatment is important, because both ICH and SAH lead to poor prognosis and severe psychomotor disability.

In a present study we review results of studies and try to explain the potential pathomechanism of statin use in hemorrhagic strokes.

2. Intracerebral hemorrhage

Intracerebral hemorrhage constitutes about 10% of strokes, leads to severe neurological deficit and mortality remains as high as 30–50% [4]. In everyday practice there is such a common notion that statins increase the ICH risk, which was justified by the results of some studies [5,6]. It is likely that such an opinion was unearthed by the results that showed connection between higher risk of ICH and low cholesterol level, but not between statins. These results were included in

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the stroke treatment guidelines in the year 2011 [7]. In the meta-analysis published in 2011 it was unequivocally presented that statins do not increase the ICH risk [8]. Similar conclusions were enclosed in the later meta-analysis in 2012 [9]. Moreover, post-ICH statin use is not associated with an increased risk of ICH recurrence [10].

Unfavorable effects of ICH are connected with initial mechanical injury produced by the hematoma and further damage that is believed to occur after the bleeding stops and called as the perihematomal edema (PE). Hematoma enlargement was seen for up to 2 days and almost always occurs within the first few hours. Clinical deterioration in subacute period is provoked by the progression of PE, increase of intracranial pressure and the risk of herniation. The late edema progression occurs in the second and third week after ICH. PE is responsible for about 75% of mass effect [11]. Significant midline shift (>3 mm) was reported in 62% of patients [12].

The formation of edema after ICH follows three distinct temporal phases: in the first hours after ICH, retraction of the clot begins. As the coagulation cascade becomes activated over the following 24–48 h, thrombin becomes activated and promotes edema formation and further disruption of the integrity of the blood–brain barrier (BBB). The third phase of edema formation starts when red blood cells in the hematoma begin to lyse, and hemoglobin with its degradation products are deposited into the brain parenchyma, thus initiating a potent inflammatory reaction. One presumed function of hemoglobin degradation products is the generation of reactive oxygen (ROS) and nitrogen species that would lead to lipid peroxidation, carboxylation, and tyrosine nitrosylation of proteins as well as eventual uncoupling of mitochondria.

An additional contributor to neuronal death is the increased presence of cytokines. Elevated levels of interleukin-6 (Il-6) and Il-10 have been associated with ICH and edema formation. Components of the complement (C) system have also been found in the perihematomal area. The presence of C3d and C9 have been documented in the parenchyma [12].

Mechanisms that trigger pathophysiological changes in and around the hematoma are linked to the role of thrombin and iron, released upon red blood cell (RBC) lysis, as 2 major factors causing brain injury after ICH. Thrombin causes brain damage at high concentrations and induces neuroprotection at low concentrations. Thrombin-induced brain injury may be mediated by the complement cascade. Thrombin activates matrix metalloproteinase-2 (MMP-2) in endothelial cells and tumor necrosis factor- α (TNF- α), which is one of the major proinflammatory cytokines. Matrix metalloproteinases are members of a family of zinc-dependent proteases that can degrade extracellular matrix and cause blood–brain barrier disruption [13]. Among 23 types of MMP's several of them were proved to play a role in the pathogenesis of ICH (MMP-2, 3, 9, 12). Increased level of MMP-3 is associated with mortality, both MMP-9 and 3 are related to residual cavity volume [14]. Increased level of TNF- α , Il-6 and MMP-9 in the first day after ICH is associated with the size of PE and subsequent enlargement of the hematoma [15].

Development of inflammatory process is connected with microglia activation and presence of leukocytes and macrophages. Neutrophils infiltration in and around hematoma

takes place after 4 h, with the peak at day 2–3, remitting within 7 days after ICH. Neutrophils may disrupt neurons directly by the ROS or indirectly, by proinflammatory proteases activation. Microglial cells monitor the well-being of their environment, being able to respond to signs of homeostatic disturbance with a program of supportive and protective activities, to safeguard innate defense mechanisms, or to assist in specific immune reactions. There are many molecules involved in the inflammatory reactions in the central nervous system: TNF- α , the interferons (IFN), Il-1, -2, -3, -4, -6, -10, -12, -15, -18, transforming growth factor β (TGF- β), colony-stimulating factors (CSF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factors (IGF), and neurotrophic factors such as nerve growth factor (NGF), neurotrophins (NT-3 and -4), or brain-derived neurotrophic factor (BDNF). The principal sources of cytokines in the brain are activated microglia/macrophages. Cytokines can be also released by many cell types, including microglia, astrocytes, neurons and endothelial cells. Nevertheless, evidence also supports the involvement of peripherally derived cytokines in brain inflammation. After ICH in humans, the blood–brain barrier permeability increases. Therefore, peripherally derived mononuclear phagocytes, T-lymphocytes, natural killer cells, and polymorphonuclear neutrophilic leukocytes, which produce and secrete cytokines, can all cross the BBB and contribute to brain inflammation [16,17].

In ICH and ischemic stroke patients levels of inflammatory cytokines change in the course of the disease. The serum level of Il-6 was most markedly elevated in the patients with acute stroke and tended to decrease thereafter. However, its level remained significantly elevated even at day 7. The level of TGF- β was significantly decreased at day 1 and day 3 and tended to return toward the control value thereafter. Il-6 has both proinflammatory and immunomodulatory actions. TGF- β plays mainly an immunomodulatory role in pathological conditions with a significant antagonistic effect against proinflammatory cytokine TNF- α [18]. Increased levels of Il-6 and Il-10 on the second day after ICH are associated with consciousness disturbances severity [19].

ROS are generated as by-products of cellular metabolism primarily in mitochondria, by neutrophils, endothelium and activated microglia. They are produced while electrons are leaking the respiratory chain and thus the amount of ROS formed, has been reported to be proportional to partial pressure of oxygen in the tissue. In addition to the mitochondrial electron transport chain, there are other ROS producing mechanisms, e.g. system of cytochrome P-450, oxidative enzymes, such as endothelial xanthine oxidase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, myeloperoxidases (MPO) of phagocytic cells, and arachidonate oxygenases. ROS have cytotoxic effects leading to cell destruction and degradation. They act both in ischemic and hemorrhagic damage to the brain [20].

The aim of ICH treatment should be the decrease in secondary ischemia, edema and intracranial pressure, as well as providing oxygen supply and optimizing cerebral metabolism. The treatment of ICH is still unsatisfactory, beside many conducted trials. Thus, new mechanisms of existing drugs should be considered and the use of new drugs should be tested.

Statins, 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors have pleiotropic properties acting on elements of immune system [21]. They inhibit inflammation, ROS development and clot forming. These drugs activate endothelium, nitric oxide (NO) availability, promote angiogenesis, neurogenesis and synaptogenesis. In the animal model atorvastatin exhibited significant increase in vascular endothelial growth factor (VEGF), endogenous cell proliferation and increase in the level of synaptic protein (synaptophysin). These data indicated that atorvastatin induced brain plasticity and has neurorestorative activity [22].

In the animal model, simvastatin treatment was proved to decrease tissue loss and hematoma volume after 4 weeks, but there was no such an effect in relation to atorvastatin. The use of those statins was associated with decreased neurological deficit and greater proliferation activity of neurons. More evident and faster effect was observed in simvastatin group [4]. Atorvastatin promotes synaptogenesis and decreases severity of neurological deficit after ICH [23]. Differences between types of statins may be connected with the fact, that simvastatin in a higher extent crosses the BBB and has more evident neuroprotective properties [24].

Another animal model study showed that atorvastatin has no effect on reduction of hematoma volume, but there was observed the reduction of hemispheric atrophy and decreased expression of the inducible nitric oxide synthase (iNOS), MPO and microglia. Atorvastatin increased endothelial nitric oxide synthase (eNOS) expression and sensorimotor recovery after experimental ICH in a dose-dependent manner [25]. Brain damage is associated with apoptosis, which is stimulated by apoptotic signaling molecules Fas ligand (FasL) and TNF, microglia, iNOS and probably by thrombin [26]. Thus, inhibiting iNOS by statins may be one of the factors preventing the brain atrophy.

Statins inhibit cytokines infiltration after ICH, such as TNF- α and IFN- γ [25].

Guanosine triphosphate (GTP) binding proteins, such as Rho, Rac and Ras undergo isoprenylation. This process affects leukocytes ability to cross BBB and may be inhibited by statins [27].

Statins inhibit ROS production by downregulation of angiotensin-1 receptor gene expression and by inhibition of GTPase Rac1 which is critically involved in the activation of NADPH oxidase by preventing the geranylgeranyl-dependent translocation of Rac1 from the cytosol to the cell membrane. In addition, statins upregulate eNOS via inhibition of geranylgeranylation of the small G-protein Rho. Antioxidative properties are also associated with stimulation of catalase, superoxide dismutase (SOD), thioredoxin and heme oxidase-1 [28]. The upregulation of eNOS and subsequent increased bioavailability of NO is one of the most important pleiotropic effects of statins. Several crucial functions such as vasodilation, as well as antiinflammatory, profibrinolytic, antiaggregant, antioxidant, and antiapoptotic effects are tightly connected to the endothelium and the release of NO. NO also has been shown to promote neo-angiogenesis and to stimulate endothelial progenitor cells in the bone marrow, supporting reendothelialization and vascular remodeling after vascular damage [29].

The problem of statin discontinuation was highlighted for the first time in acute coronary syndrome and then in stroke

patients [21]. There is pathological evidence of possible harmful rebound reaction after withdrawal of statins in stroke patients. Chronic intake of statins blocks isoprenoid-dependent Rho membrane translocation and GTP-binding activity and thus leads to accumulation of non-isoprenylated Rho protein in the cytosol. Withdrawal of atorvastatin restores the availability of isoprenoids, results in a massive membrane translocation and activation of Rho, causing downregulation of endothelial NO production. Two days after the withdrawal of statin treatment, endothelial NO production decreases up to 90% [30].

Discontinuation of statins after onset of symptoms completely abrogates its beneficial effect and this could be due to the rebound effect on NO [31]. In ICH patients there was revealed relationship between in-hospital statin discontinuation and stroke severity and 30-day mortality [32].

Previous studies indicate possible beneficial effect of statin use in acute phase in animal models. The prospective studies of the statin use in the acute phase of ICH in humans has not been provided yet. There has only been one retrospective analysis made [40]. Studies regarding the preadmission statin use and ICH outcome are listed in Table 1.

3. Subarachnoid hemorrhage

Subarachnoid hemorrhage is connected with mortality as high as 46% and severe psychomotor disability, with incidence of 2–32/100,000. After aneurysmal SAH, angiographic vasospasm is seen in 30–70% of patients, with a typical onset from 3 to 5 days after the hemorrhage, maximal narrowing at 5–14 days, and a gradual resolution over 2–4 weeks [41,42].

Prominent complication of SAH is delayed ischemic neurological deficit (DIND) or delayed cerebral ischemia (DCI), which is a major cause of disability and mortality, with prevalence of 33–38%. It can lead to focal neurological deficit or death. Symptoms can be reversible or progress into complete stroke confirmed by neuroimaging tests in 10–13% cases. DIND is associated with worse prognosis, its severity correlates with the volume of extravasated blood. The explanation may be vasospasm or spreading of cortical depolarization [43]. Another hypothesis of DIND is the early cerebral autoregulatory failure [44].

It is believed that the most important role in the pathogenesis of vasospasm plays the depletion of NO, which is a potent vasodilator. Other theories postulate that the presence of extravasated hemoglobin and its degradation products may disrupt signaling between the vascular endothelium and the underlying smooth muscular layer. This latter process induces a cascade of metabolic events, which finally leads to endothelin-1 (ET-1) production and cerebral vasoconstriction. ET-1 is a potent vasoconstrictor and is produced when ischemia occurs. Its increased level in the plasma and CSF (cerebrospinal fluid) correlates with the persistence of cerebral vasospasm. Another mechanism proposed to be implicated in the development of cerebral vasospasm is the free radical oxidation of bilirubin to bilirubin oxidation products and inflammatory state due to leukocyte recruitment.

Adhesion molecules, such as ICAM-1 (intercellular adhesion molecule-1), VCAM-1 (vascular cell adhesion molecule-1) and E-selectin, have been found to be elevated in the CSF.

Table 1 – Studies regarding the association between statin use and ICH.

Study	Number of ICH patients	The association that was evaluated	The effect of statin use
Dowlatsahi et al. [32]	2466	Preadmission statin use with outcomes (severity of stroke at presentation, mRS at discharge, 30-day mortality, and 6-month mortality)	No association
Fitzmaurice et al. [10]	629	Preadmission statin use with 90-day outcomes and mortality	No association
Fitzmaurice et al. [10]	79	Post-ICH statin use with the risk of recurrence	No association
King et al. [33]	1381	Preadmission statin use with 30-day mortality	No association
Biffi et al. [34]	2521	Preadmission statin use with 90-day functional outcome and mortality	Favorable outcome and reduced mortality
Leker et al. [35]	312	Preadmission statin use with stroke severity and outcomes	Lower baseline NIHSS, less systemic complications; reduced mortality and neurological disability
Naval et al. [36]	314	Preadmission statin use with 30-day mortality and outcomes at discharge	No association between functional outcome; decreased mortality
Naval et al. [37]	125	Preadmission statin use with volume of perihematomal edema on initial head CT	Reduced volume of perihematomal edema
Ricard et al. [38]	303	Preadmission statin use with ICH volume variation of first follow up CT scans and death	Increased baseline ICH volume, increased progression of ICH volume; no association with mortality
Woo et al. [39]	1578	Preadmission statin use with risk of ICH in association with Apolipoprotein E (ApoE) polymorphisms	Higher risk for lobar ICH in ApoE4/E4 and ApoE2/E4 genotypes
Niewada et al. [40]	3111	Preadmission and in-hospital statin use with outcomes and mortality	Preadmission use: higher in-hospital mortality; in-hospital use: lower in-hospital mortality

Cytokine expression is profoundly altered following SAH. Several cytokines have been found to be upregulated in cerebral vasospasm, including TNF- α , IL-1, IL-6, and IL-8 [45].

Statins can prompt a beneficial activity in SAH, because they inhibit transvascular migration and proliferation of leukocytes, activity of ICAM-1, VCAM-1, IL-1b, IL-6, IL-8 and TNF- α . The antioxidative effect is also of clinical importance [21,46,47].

The definition of DCI had not been unambiguous, because the pathomechanism of vasoconstriction in SAH is not clear. A multidisciplinary research group proposed the definition of DCI as follows: a clinical deterioration caused by DCI is the development of focal neurological signs, such as aphasia or hemiparesis, and a decrease of 2 points in the level of consciousness in the Glasgow Coma Score. This should last for at least 1 h, should not be apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT (computed tomography) or MRI (magnetic resonance imaging) scanning of the brain, and appropriate laboratory studies. The use of the word “vasospasm” should be restricted to descriptions of a radiological test and not applied to clinical manifestations of DCI [48].

Statins inhibit NADPH oxidase, superoxide production and upregulate the expression and activity of eNOS, which improves endothelial reactivity and cerebral blood flow [28].

Other effects of statins possibly beneficial in SAH were cited above [22].

In a case study it was suggested that there was an inverse relationship between the use of statins and risk of cerebral aneurysm rupture [49].

On the other hand statin users have a higher risk for subarachnoid hemorrhage-related vasospasm, but authors suggested that the underlying cause of this observation could be the abrupt statin withdrawal [50].

Acute pravastatin treatment after SAH reduces traditional rescue therapy for vasospasm after aneurysmal subarachnoid hemorrhage, improves cerebral autoregulation and reduces DIND [51]. Improvement in early outcome has proved robust at 6 months, particularly in relation to physical and psychosocial outcome [52].

A meta-analysis including 158 patients showed that statin therapy after aneurysmal SAH significantly reduces the incidence of vasospasm (relative risk [RR] = 0.73; 95% CI, 0.54–0.99), DIND (RR = 0.38; 95% CI, 0.17–0.83) and mortality (RR = 0.22; 95% CI, 0.06–0.82) [53].

In contradiction to these results, a meta-analysis including four, only randomized trials, showed no effect of pravastatin and simvastatin in SAH patients, but the total number of subjects was only 190 and two of analyzed studies were identical to the prior paper [53,54]. A new randomized study with 38 SAH patients showed no beneficial effect of simva-

statin treatment in terms of reduction in clinical vasospasm, mortality or improved functional outcome [55]. More information about statin treatment will be given after completing the STASH (Simvastatin in Aneurysmal Subarachnoid Hemorrhage) study with the use of simvastatin in 1600 patients. Initial results of that study demonstrate potential benefits [56].

There is no exact time when statin treatment should be introduced, but in cited studies it took place within first 96 h after SAH. Vasospasm initiates since forth day after the onset, so the time of first 96 h seems to be reasonable.

4. Conclusions

Taking into consideration the serious outcomes, mortality, psychomotor and verbal deficits in both ICH and SAH patients, searching for new therapeutic options is desirable. The unquestionable role of inflammatory factors in the pathogenesis of these disorders justifies considering statin treatment. Previous results are contradictory, but questions concerning beneficial effects are probably due to small samples count.

More studies on greater groups are indispensable with taking into account physicochemical properties and dose of particular statins, that can affect the ability of central nervous system penetration [57].

The important issue is the dosing of statins. High-dose versus usual-dose statin therapy in coronary artery disease is beneficial for high-risk patients [58]. There are several studies that confirmed dose-depending effects of statins, even in all ischemic stroke subtypes, but it is not fully known presently if higher doses of statins should be used in ischemic stroke patients [59,60]. The disparate findings of the Medical Research Council/British Heart Foundation Heart Protection Study (HPS) and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trials suggest that careful selection of patients with atherosclerotic stroke is critical for realizing a benefit to statin treatment [61].

In ICH patients the effect of statins did not alter results after adjustment for statin dose [34,42] or such an information was not presented [35,36].

There are limited data available regarding the statin dosing in SAH patients. A potentially beneficial effect was observed after the use of pravastatin at dose of 40 and 80 mg [51,52]. The beneficial or no effect was observed with the use of simvastatin 80 mg [53–55]. The potential role of dose and type of statins needs explanation and more attention to be paid in the future studies.

Conflict of interest

Authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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